Remarks

Claims 59, 61-66, 68-115 are now in the case. Claims 60 and 67 have been cancelled. Claims 112-115 have been added. Support for the added claims can be found in the claims as originally filed and throughout the specification, see in particular pages 4-10.

Rejection under U.S.C. 112, first paragraph (New Matter)

Claims 60 and 67 were rejected under 35 U.S.C. §112, first paragraph, as being considered to contain matter that was not described in the specification.

Applicants respectfully traverse these grounds for rejection. However, merely to advance prosecution towards allowance, claims 60 and 67 have been cancelled.

Applicants respectfully submit that for at least the reasons stated above, the rejection of claims 60 and 67 under 35 U.S.C. §112, first paragraph (New Matter), has been rendered moot and withdrawal of the rejection is respectfully requested.

Rejection under U.S.C. 112, first paragraph (Enablement)

Claims 59-111 stand rejected under U.S.C. 112, first paragraph, allegedly because the specification is not enabling.

Applicants respectfully traverse these grounds for rejection. The Action states that the term "comprising" leaves the claims open for inclusion of unspecified amino acids on either or both sides of the N- and C-terminal of the **core structure of nectin-3 polypeptide**. The Action alleges that the specification fails to provide sufficient guidance as to which amino acids outside the **core structure** of SEQ ID NOs: 4 or 6 is essential for maintenance of its nectin 1 binding activity and which amino acids can be added to the **core structure** of SEQ ID NOs: 4 or 6 and still maintain the same function, besides full length SEQ ID NOs: 2, 4, 6, 8, 10, 12 and 31. It is alleged that the claims fail the "how to make" prong. (Emphasis added)

Applicants assume that what is meant by "the core structure of nectin-2 polypeptide" is amino acid residues 58-404 (which includes residues 74-365). In the instant specification, Applicants have demonstrated that the amino acid sequences of 58-404 of SEQ ID NO:4 or 6 and 58-366 of SEQ ID NO:12 (which include amino acid residues 74-365) exhibit a variety of activities. A summary of Examples 4-6 of Applicants' specification is provided:

Example 4 discloses the binding of a polypeptide comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 and including amino acid residues 74-365) to human endothelial cells. As described in the paragraph beginning at line 29 on page 53:

> "The results show that nectin-3α-Fc binds with high intensity to proliferating HUVEC. Further activation of HUVEC by TNF α results in a 40% decrease in nectin-3α-Fc binding. HUVEC activation by PMA results in a more than 75% decrease in nectin-3α-Fc binding... Regulation of nectin-3α-Fc binding to counterstructure(s) on endothelial cells by inflammatory signals suggests that nectin-3α-Fc may play a significant biological role in endothelial cell function, motility/recruitment and extravasation during inflammatory immune response, tissue remodeling and ischemia/reperfusion conditions."

First paragraph, page 54 discloses:

> "The nectin-3α-Fc also binds with high intensity to cultured human dermal microvascular endothelial cells and to the human colon carcinoma cell line T84. Additional experiments shows that the addition of exogeneous nectin-3α-Fc to PMA stimulated MVECs can inhibit the migration of these cells. It was also determined that the recombinant nectin-3α-Fc can inhibit PMA induced kidney endothelial cell migration in wound healing assays."

Example 5 describes the inhibition of endothelial cell migration by a polypeptide comprising acid residues 58-404 of SEQ ID NOs: 4 or 6. As described in the paragraph bridging pages 54-55,

> "addition of nectin-3α-Fc at concentrations of 25 micrograms/ml to HMVEC-d...inhibited migration/hapotaxix induced by and EGM-2 gradient." "Addition of nectin-3α-Fc at a concentration of 25 micrograms/ml to the EGM-2 media gradient in the bottom well inhibited the migration of PMA-stimulated HMVEC-d by 55% compared to migration of PMA-stimulated HMVEC-d cultured in an EGM-2 gradient alone." "The data show that nectin-3α-Fc can decrease endothelial cell migration/haptotaxis *in vitro*, and indicate that nectin-3α may play a role in endothelial cell movement and vessel formation/angiogenesis *in vivo*."

Example 6 describes the activity of a polypeptide comprising amino acid residues 58-404 of SEQ ID Nos: 4 or 6 in a wound-closure assay. Endothelial cell migration is measured as the rate of closure of a circular wound.

> "The nectin-3α-Fc at 30 micrograms inhibited PMA-induced endothelial migration, reducing the rate of migration to approximately the same as observed for unstimulated cells. EGF-induced endothelial migration was inhibited by nectin-3α-Fc in a concentration dependent manner." Lines 30-32, page 55.
>
> Nectin-3 staining on cell monolayers provided "the first demonstration that nectins are localized in the cell surface in structures other than the adherens junctions. It is also markedly different than the other cell junction proteins that were immunolocalized in these wound assays...This is the first indication that the nectins may play a role in the cell's activity in a capacity other than in organizing cell junctions." Paragraph bridging pages 55-56.

The Action acknowledges that the specification **is enabling** for a substantially purified polypeptide comprising an amino acid of SEQ ID NO:2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO: 4, 6, 10, 12 and 31 comprise amino acids 74-152, 189-250 and 287-342. SEQ ID NO: 13-16 are also acknowledged as enabled. Within this group of acknowledged enabled sequences the "core structure" is coupled to a host of N- and/or C-terminal extensions of various lengths and complexity including: complete signal sequences, signal sequences lacking N-terminal amino acid residues, signal sequences with murine substituted sequences, transmembrane domains, cytoplasmic domains, Fc regions from human IgG1, and small peptide affinity tags such as FLAG and His tags. Given that the core structure has demonstrated independent biological activity, the N- and C-terminal extensions of these enabled sequences cannot be considered to interfere with the function of the "core structure of nectin-3". The Action provides no evidence to indicate that any other similar N- or C-terminal extensions would negate the demonstrated biological activity of the "core structure".

Even if, assuming *arguendo*, that an extension, such as a peptide tag or linker, adversely affected the biological activity, the tagged or linkered polypeptide would still be useful for raising antibodies, either by immunization with the complete peptide fusion or with proteolytic fragments thereof. Production of antibodies, including monoclonal antibodies, is routine in the art. Methods for making anti-nectin-3 antibodies, including immunization with small peptide immunogens, are disclosed in Applicants' specification at pages 23-24.

Applicants submit that they have met their burden to provide a specification that described any method of making and using the claimed invention that bears any "reasonable correlation" to the entire scope of the claims. Applicants' specification teaches how to make and use polypeptides comprising the claimed amino acid residues.

With specific regard to claims 79-111, the Action states that "in order to satisfy U.S.C. 112 1st paragraph, the specification must teach how to make and use the invention, not how to identify the invention." (paragraph bridging pages 5-6, emphasis added). Action alleges that until the time when at least about 80% - 99% sequence identity polypeptides are found, then one of skill in the art cannot make them (paragraph bridging pages 5-6).

Applicants fail to see how identifying differs from finding the sequences. One of skill in the art, using only a pencil and paper and the sequences provided in Applicants' invention, can produce a list of sequences having the required identity to Applicants' claimed sequences. The mere substitution of three alanine residues for any three amino acid residues within the sequence of amino acid residues 58-404 creates a sequence that is 99% identical across the

length of that sequence as required by Applicants' claimed invention. In addition, known sequences can be compared to the sequence of amino acid residues 58-404 of SEQ ID NOs: 4 or 6, for example, to determine whether or not the sequence is about 80-99% identical over the length of the claimed sequence. As described in the previous response, computer programs and algorithms are known in the art and commercially available for making such determinations and are described within Applicants' specification, see pages 15-16. One of skill in the art can easily and quickly determine whether any sequence in question would fall within the scope of the sequences of the claimed invention. As such, the sequences are now "found".

The Action states "the specification fails to provide sufficient guidance as to which amino acid of SEQ ID NO: 4, 6, 10, 12 and 31 are essential for maintaining the biological activity and which changes can be made in the structure of SEQ ID NO: 4, 6, 10, 12 and 31 and still maintain function." Paragraph bridging pages 5 and 6.

The claims are directed to polypeptides having at least 80% amino acid identity across the length of amino acid residues 58 through 404 of SEQ ID NO: 4 or 6. Claims 86 and 93 are similar in recitation. The requirement for identity is limited to a specific and identified sequence, in this case amino acid residues 58 through 404, not across the entire sequence of SEQ ID NOs: 2, 4, 6, 8, 10, 12 and 31. One of skill in the art may rely on various tools and skills when analyzing sequences, for example, alignment of the sequence in question with homologous sequences to determine which residues are conserved and where substitutions, deletions, additions are made and tolerated. Table 2 of the instant specification provides such an alignment of related nectin sequences identifying conserved residues and providing a consensus sequence (page 6, starting at line 22). Assays are provided to confirm the endothelial cell migration inhibition activity of the polypeptides. As discussed above, claims to a polypeptide comprising an identified "core structure" having various N- and C-terminal extensions were acknowledged as enabled and were not considered to negate the biological activity of the core structure. The polypeptides encompassed within claims 79-111 are no different.

The Action further alleges "[w]hile experiential testing techniques using cell adhesion compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure." (page 6, first full paragraph)

What is required is a reasonable expectation for success and Applicants have provided such in Examples 5 and 6. Polypeptides of the claimed invention were shown to have inhibitory properties. Endothelial cell migration assays are routinely used to characterize

proteins or polypeptides of interest. A search of the term "endothelial cell migration" on Medline turns up hundreds of references that describe use of endothelial cell migration assays to identify related biological activities of proteins and polypeptides. The abundant use of such assays is a clear indication that those of skill in the art widely and routinely use such assays to identify properties of particular proteins in question, to compare the protein to other proteins, and to confirm and further characterize protein activity. Such assays have been used to screen large numbers of unrelated proteins to determine which have the desired activity and would be the subject of further experimentation. Applicants have demonstrated that such assays are useful in identifying desired activities of the claimed polypeptides and those assays are routinely used by those of skill in the art. Without more there is no basis to believe that one of skill in the art would not have a reasonably expectation of success.

As to Skolnik et al., the problems faced by annotators are not at issue in this invention. Applicants have demonstrated activity and function associated with the claimed nectin-3 polypeptides. Such results have been extensively discussed above and are provided in Examples 3-6.

Applicants respectfully submit that for at least the reasons stated above, the rejection of claims 59-78 under 35 U.S.C. §112, first paragraph (enablement), has been overcome and withdrawal of the rejection is respectfully requested.

Rejection under U.S.C. 112, first paragraph (Written Description)

Claims 59-111 are rejected under U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Action alleges that:

> "there is **no described** or art-recognized **correlation or relationship between the structure of the invention, the core structure of nectin 3 and it's inhibition of endothelial cell migration function, the feature deemed essential to the instant invention**. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of polypeptides comprising the core structure of nectin 3 which retain the features essential to the instant invention". (emphasis added) Page 7, last paragraph of section 8.

Applicants respectfully traverse these grounds for rejection. Applicants wish to direct attention to Examples 3, 4, 5 and 6 of the specification where there is abundant description of the correlation or relationship between the structure of the invention, the core structure of

nectin 3 and it's inhibition of endothelial cell migration, as well as other activities. By "core structure" Applicants assume the Action refers to amino acid residues 58-404 that are associated with the extracellular domain of nectin-3 which also include amino acid residues 74-365 that comprise the three Ig domains found within the nectin-3 extracellular domain. Example 3 discloses construction and expression of soluble Nectin-3-Fc polypeptides (see in particular the paragraph beginning at line 15 on page 52). The soluble nectin-3-Fc polypeptides consist of the extracellular domain of the nectin-3 fused to the Fc portion of a human IgG1 and optionally, the nectin-3 signal sequence to facilitate expression. The extracellular domain of nectin-3α comprises amino acid residues 58-404 of SEQ ID NO: 6 and the extracellular domain of nectin-3 β comprise amino acid residues 58-366 of SEQ ID NO: 12, which includes amino acid residues 74-365 (which encode the three IgG domains found within the nectin-3 extracellular domain). See example 3, page 56 and pages 4 and 5 for descriptions of the extracellular domains and construction of nectin-3 extracellular domain-Fc polypeptides. Such soluble nectin-3 extracellular domain-Fc polypeptides are disclosed in SEQ ID NOs: 13 and 14.

As described in detail above, Example 4 discloses the binding of the soluble nectin-3 extracellular domain-Fc fusion polypeptide (as described above and disclosed in SEQ ID NO:13, comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 and including amino acid residues 74-365) to human endothelial cells.

Also described in detail above, Example 5 describes the inhibition of endothelial cell migration by the nectin-3-Fc fusion polypeptide comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6.

Lastly, Example 6 describes the activity of the Fc fusion polypeptide comprising amino acid residues 58-404 of SEQ ID Nos: 4 or 6 in a wound-closure assay as described in detail above. Endothelial cell migration is measured as the rate of closure of a circular wound.

Contrary to the Action's assertion, the instant specification does describe a correlation or relationship between the structure of the invention, the core structure of nectin 3 (amino acid residues 58-404 of SEQ ID NOs: 4 or 6 including residues 74-365) and it's inhibition of endothelial cell migration function, a feature deemed essential to the instant invention. Example 4 describes the binding of a polypeptide comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 to human umbilical vein endothelial cells, human dermal microvascular endothelial cells and to the human colon carcinoma cell line T84. Example 5 describes the inhibitory activity of this polypeptide on endothelial cell migration. Example 6 further

demonstrates the inhibitory activity of the polypeptide comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 and goes beyond by providing a first indication of a role for nectin in organizing cell junctions.

Applicants respectfully put forth that without some evidence to the contrary, one of skill in the art could envision the claimed genus of polypeptides comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 (which includes amino acid residues 74-365). A genus may be described via "recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." (University of California v Eli Lilly and Co., 119 F.3d 1559, 1569) Applicants once again point out that such a description can take the form of "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics." (Guidelines for Examination of Patent Applications under 35 U.S.C. §112, First Paragraph (Written Description) Requirement, 66 Fed. Reg. 1099, at 1106).

The complete amino acid sequences of nectin-3 α, β and γ have been described in the application, SEQ ID NOs: 2, 4, 6, 8, 10, 12 and 31, see the Sequence Listing. Polypeptides of the claimed invention share amino acid residues 58-404 of SEQ ID NO:4 or 6 which include amino acid residues 74-365. Thus Applicants have provided a structural feature that is common to the genus made up of polypeptides possessing amino acid residues 58-404 or 74-365 which are identical in the structure set forth in SEQ ID NOs: 4, 6, 10, 12 and 31.

Applicants' specification describes particular physical features of SEQ ID NOs: 4, 6, 10, 12 and 31 (see for example pages 4-7) where the signal sequence, extracellular, transmembrane and cytoplasmic domains are identified and described in association with their location within SEQ ID NOs: 4, 6, 10, 12 and 31. Such structural features are common to the nectin polypeptide family, see page 4-10, for example. Polypeptides of the claimed genus share amino acid residues 58-404 (including residues 74-365) which correspond to the extracellular region. Thus Applicants' specification has provided structural features that are common to the genus made up of polypeptides comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 (which includes residues 74-365 of SEQ ID NOs: 10, 12 and 31).

As discussed above in more detail, Applicants' specification provides known or disclosed correlations between functional characteristics and structure characteristics common to the genus of claimed invention. Soluble polypeptides comprising amino acid residues 58-404 of SEQ ID NO: 4 or 6 were shown to bind to human umbilical vein endothelial cells, human dermal microvascular endothelial cells and to the human colon carcinoma cell line

T84. The inhibitory activity of these soluble polypeptides was demonstrated by endothelial cell migration and wound healing assays.

To summarize, Applicants' specification describes structural features common to the genus of polypeptides of the claimed invention. Such features have been described by:

(a) complete and/or partial structure, such as polypeptides comprising amino acid residues 58-404 of SEQ ID NOs:4 or 6 (which include residues 74-365 of SEQ ID NOs: 10, 12 and 31) as well and the complete structure of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 15, 16 and 31, and additionally the soluble polypeptides comprising amino acid residues 58-404 or amino acid residues 58-366 as disclosed in SEQ ID NOs: 13 and 14;

(b) physical properties, such as extracellular, transmembrane and cytoplasmic domains of SEQ ID NO:2, 4, 6, 8, 10, 12, and 31; and

(c) functional characteristics coupled with known or disclosed correlation between function and structure, such as the association of polypeptides comprising amino acid residues 58-404 of SEQ ID NOs: 4 or 6 with inhibition of cell migration.

Applicants' specification provides description of structural features common to the members of the claimed genus. These features constitute a substantial portion of the genus. This recitation comes in the form of not only a description of complete and/or partial structures, but also identification of physical properties and functional characteristics coupled with known or disclosed correlations between the function and structure of the polypeptides of this genus.

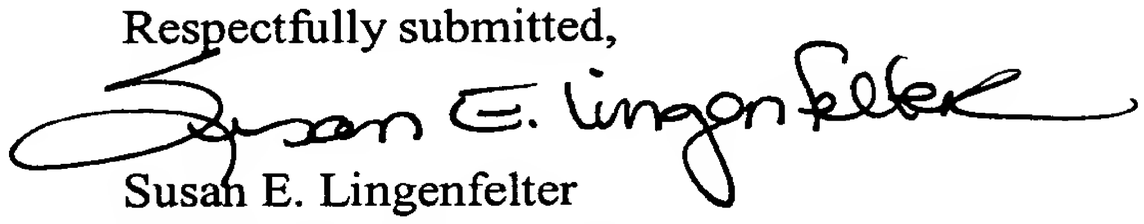
Applicants have provided disclosure related to **all** of the factors that evidence possession of a claimed invention according to the Guidelines for Examination. According to the Guidelines <u>any combination of such identifying characteristics</u> that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. Applicants submit that one of skill in the art would clearly recognize that Applicants were in possession of the claimed genus based upon their own knowledge of nectin polypeptides and the disclosure provided in the specification. Applicants' specification therefore meets the requirements as set out in the Guidelines for Examination for written description.

Applicants respectfully submit that for at least the reasons stated above, the rejection of claims 59-78 under 35 U.S.C. §112, first paragraph (written description), has been overcome and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants submit that the presented claims are in condition for allowance. A favorable action is earnestly requested. Applicants' attorney invites the Examiner to call her at the number below if any issue remains outstanding.

Respectfully submitted,



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